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(54) ABSORPTION ACCELERATOR AND PERCUTANEOUS ABSORBING PREPARATION HAVING THE SAME

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a percutaneous absorption accelerator and a percutaneous absorbing preparation containing the same and contriving high skin permeability of effective component and stabilization of a base physical property.
SOLUTION: This invention relates to a percutaneous absorption accelerator comprising hexylene glycol and 1-methol, more precisely a percutaneous absorption accelerator of a female hormone or its derivative. Further, this invention is composed of a base component comprising a styrene-isoprene-styrene block copolymer and/or polyisobutylene, a softener and a tackiness imparting agent, and a hormone agent, especially estrogen and/or gestagen as an effective component and hexylene glycol and 1-menthol as percutaneous absorption accelerators.

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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] Absorption enhancers which consists of hexylene glycol and l-menthol.
[Claim 2] Absorption enhancers according to claim 1 whose hexylene glycol is 1 - 10 % of the weight and whose l-menthol is 0.1 - 7 % of the weight to the pharmaceutical preparation whole quantity.
[Claim 3] Hexylene glycol: The basis for percutaneous absorption pharmaceutical preparation according to claim 1 or 2 whose rate of l-menthol is 1:0.1-1:7.
[Claim 4] The basis for percutaneous absorption pharmaceutical preparation according to claim 1 to 3 to which the basis component used the styrene-isoprene-styrene block copolymer and/or the polyisobutylene, the softener, and the tackifier as the indispensable component, and made hexylene glycol and l-menthol absorption enhancers.
[Claim 5] The basis for percutaneous absorption pharmaceutical preparation according to claim 2 to 4 to which a basis component comes to blend the absorption enhancers with which a softener considers 20 - 60 % of the weight ten to 60% of the weight two to 10% of the weight, a tackifier considers as an indispensable component, and 10 - 40 % of the weight of styrene-isoprene-styrene block copolymers and a polyisobutylene become this from 1 - 10 % of the weight of hexylene glycols, and 0.1 - 7 % of the weight of l-menthol.
[Claim 6] Percutaneous absorption pharmaceutical preparation according to claim 4 to 5 which comes to contain a drug as an active principle.
[Claim 7] Percutaneous absorption pharmaceutical preparation according to claim 4 to 6 whose drugs are estrogen and/or corpus luteal hormone.
[Claim 8] Percutaneous absorption pharmaceutical preparation according to claim 7 whose estrogen is estradiol and its derivative and the loadings of whose are 0.1 - 5 % of the weight.
[Claim 9] Percutaneous absorption pharmaceutical preparation according to claim 7 whose corpus luteal hormone is norethisterone, acetic-acid norethisterone, and its derivative and the loadings of whose are 0.5 - 10 % of the weight.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to the percutaneous absorption pharmaceutical preparation which made hexylene glycol and l-menthol contain as absorption enhancers about the field of endermic medication. By using hexylene glycol and l-menthol for a detail as a styrene-isoprene-styrene block copolymer, a softener, a tackifier, and absorption enhancers more at a basis component, it is the percutaneous absorption pharmaceutical preparation which made skin permeability of a drug good, and the drugs of a quantum are beforehand related with the percutaneous absorption pharmaceutical preparation characterized by to be accuracy and being certainly applicable to a patient.

[0002]

[Description of the Prior Art] The estradiol contained in estrogen is secreted from the ovary at the stage when it can reproduce female. Therefore, the woman before and behind a menopause mainly causes lack of estradiol, and symptoms, such as menopausal disorders and an emmeniopathy, produce her. Although the cure by oral agent administration etc. is performed for the object which improves these symptoms now, since alimentary canals, liver, etc., such as the stomach and intestines, are metabolized promptly and inactivation is carried out, in order to expect sufficient drug effect manifestation, high-dose estradiol must be taken. Moreover, there is a possibility that manifestation nature, such as a side effect, may increase for a high dose.

[0003] Then, the attempt with which is going to lessen the metabolic turnover of estradiol by dermal administration, and tends to be made to reach into blood, and it is going to present a therapy is made. Examination which is made to absorb from transderma the corpus luteal hormone which is other hormone on the other hand, and suppresses the side effect in estradiol administration is also made. The percutaneous

absorption pharmaceutical preparation which uses estradiol and corpus luteal hormone as a drug effect component at JP,4-342532,A, and uses as a principal component the acrylic binder which consists of 2-ethylhexyl acrylate and an N-vinyl-2-pyrrolidone as a binder is proposed. However, drug release nature is low, and the stimulus to the skin of an acrylic binder is strong, and it is intolerable to long-term repetitive administration.

[0004] Moreover, the gel which consists of hydroxypropylcellulose and ethanol is made to dissolve the estradiol and acetic-acid norethisterone which are a drug effect component in JP,6-51623,B, this is made into a reservoir mold, and the approach of controlling bleedoff of a drug effect component by the permeability accommodation film is proposed. However, ethanol had a problem in side effects, like the rubor arises by the frequency where skin irritation is strong and high to a pasting part etc. On the other hand, the percutaneous absorption patches which consist of a styrene-isoprene-styrene block copolymer which used crotamiton as a resolvent are proposed by the international disclosure WO 91/No. 17752 official report and JP,5-148145,A. However, when crotamiton was used for the resolvent, the problem was in stability -- the cohesive force which the styrene-isoprene-styrene block copolymer itself was dissolved in crotamiton, and was expected is not acquired.

[0005] Hexylene glycol (generic name.) The 2-methyl -2 and 4-pentanediol are usually used for softeners, such as a moisturizer, a solvent, an industrial use cleaning agent, a water pressure fluid, and leather fiber, and a softening agent, the agent for ink, the agent for photographs, etc. for a chemical name. The external preparations which used hexylene glycol as an antimicrobial agent are proposed by JP,7-109220,A and JP,8-53338,A. Moreover, the external preparations which used hexylene glycol as absorption enhancers are proposed by the international disclosure WO 96/No. 19976 official report and JP,7-138153,A. However, hexylene glycol needed to blend hexylene glycol so much, in order to acquire absorption facilitatory effect with it. [high compatibility with an acrylic basis, and] [sufficient] Furthermore, problems, such as bringing about effect, were in the adhesive lowering by abundant combination of hexylene glycol, and the fundamental physical properties of pharmaceutical preparation.

[0006]

[Problem(s) to be Solved by the Invention] this invention persons result in completion of this invention, as a result of continuing examination wholeheartedly for the purpose of offering the percutaneous absorption pharmaceutical preparation or the basis which attained stabilization of high skin permeability 2 basis physical properties of 1 drug effect component in view of the above trouble.

[0007]

[Means for Solving the Problem] this invention persons found out having the percutaneous absorption acceleration operation with a high combination of hexylene glycol (a chemical name is 2-methyl - 2, 4-pentanediol) and l-menthol, as a result of repeating research wholeheartedly, in order to solve the above-mentioned technical problem. In the detail, hexylene glycol and l-menthol found out having the outstanding percutaneous absorption acceleration operation over female sex hormones, such as estrogen, corpus luteal hormone, and its derivative, or the derivative of those more. namely, the penetration enhancer with which this invention consists of hexylene glycol and l-menthol -- it is preferably related with the penetration enhancer of a female sex hormone or its derivative.

[0008] Moreover, this invention relates to the percutaneous absorption basis which comes to contain the hexylene glycol and l-menthol of the basis component for percutaneous absorption, and sufficient amount to have a percutaneous absorption acceleration operation. As a basis component for percutaneous absorption, the thing containing a styrene-isoprene-styrene block copolymer and/or a polyisobutylene, a softener, and a tackifier is desirable.

[0009] Furthermore, it resulted in header this invention that the percutaneous absorption pharmaceutical preparation which made skin permeability of a drug good was obtained by the stabilization pan of good cohesive force and pharmaceutical preparation physical properties by using a styrene-isoprene-styrene block copolymer and/or a polyisobutylene, a softener, a tackifier, hexylene glycol, and l-menthol for a detail as a basis component. This invention relates to the basis for percutaneous absorption patches which comes to contain a styrene-isoprene-styrene block copolymer and/or a polyisobutylene, a softener, a tackifier, hexylene glycol, and l-menthol as a basis component, and the basis for percutaneous absorption patches concerned and the percutaneous absorption patches which come to contain a drug.

[0010]

[Embodiment of the Invention] It is necessary to have percutaneous absorption by the activity matter physiologically about the drug used as the active principle of the percutaneous absorption pharmaceutical preparation of this invention. Or after percutaneous absorption is carried out, you may be the so-called prodrug as shows bioactive. Or the inorganic or organic addition salt permitted pharmacologically is included.

[0011] Female sex hormones, such as estrogen and a derivative of **********, are mentioned preferably as a drug of the percutaneous absorption pharmaceutical preparation of this invention. For example, as an active ingredient, as estrogen,

although estradiol, estrone, estriol, equilin, equilenins, or those derivatives are mentioned, estradiol is mainly preferably used for the percutaneous absorption pharmaceutical preparation of this invention. Moreover, as corpus luteal hormone, although progesterone, hydroxyprogesterone caproate, medroxyprogesterone acetate, dydrogesterone, chlormadinone acetate, the ethisterone, the dimethisterone, norethisterone, acetic-acid norethisterone, enanthic acid norethisterone, acetic-acid ethynodiol, the megestrol acetate, or allylestrenol is mentioned, norethisterone and acetic-acid norethisterone are mainly preferably used for the percutaneous absorption pharmaceutical preparation of this invention.

[0012] in addition -- as a drug effective in the percutaneous absorption pharmaceutical preparation of this invention -- for example, an antiemetic drug (example: -- granisetron hydrochloride --) Azasetron hydrochloride, ondansetron hydrochloride, ramosetron hydrochloride, etc., pollakiuria therapy agents (example: oxybutynin hydrochloride etc.) and calcium antagonist (example: -- nifedipine --) corticosteroid (hydrocortisone --), such as NIZORUJIPIN, nicardipine, and nit REJIPIN antiphlogistic sedative drugs (example: -- indomethacin --), such as prednisolone and clobetasol propionate Ketoprofen, flurbiprofen, felbinac, ketorolac, etc., Mesmerism depressant (phenobarbital, triazolam, nitrazepam, lorazepam, etc.), A tranquilizer (a fluphenazine, diazepam, chlorpromazine, etc.), a pit hypertension agent (clonidine, clonidine hydrochloride, pindolol, and propranolol --) Pressure-lowering diuretics, such as nitrendipine and metoprolol (hydro thiazide etc.), The quality of a pit living thing (penicillin, a tetracycline, an erythromycin, chloramphenicol, etc.), A narcotic (lidocaine, dibucaine hydrochloride, ethyl aminobenzoate, etc.), Antibacterial substances (hydrochloric-acid benzalkonium, clotrimazole, etc.), a vitamin compound (vitamin A etc.), pit epilepsy agents (nitrazepam etc.) and a coronary vasodilator (nitroglycerin --) A pit histamines agent, such as isosorbide dinitrate (diphenhydramine, chlorpheniramine, etc.), antitussive (tulobuterol hydrochloride, salbutamol, and ketotifen fumarate --) **** agents (clomipramine hydrochloride --), such as tranilast and a hydrochloric-acid isopropanal TERENO roll cerebral circulation improvement agents (dihydroergotoxine mesylate --), such as amitriptyline hydrochloride antitumor agents (5-fluorouracil etc.), such as ifenprodil, and a muscle relaxant (example: -- eperisone --) painkillers (example: a fentanyl, morphine, etc.), such as a dantrolene, and the hormone drug (Lu Tina IJINGU hormone-lily JINGU hormone (LH-RH) --) of a polypeptide system Teleangiectasia agents, such as silo tropine RIRIJINGU hormone (TRH), An immunity modifier (example: the poly saccharides, auranofin, lobenzarit, etc.), Choleretic drugs (example: ursodesoxycholic acid etc.), a diuretic (example: hydroflumethiazide etc.), The

agents for diabetes mellitus (example: tolbutamide etc.), a gout drug (example: colchicine etc.), The drug of classes, such as the anti-Parkin Son agents (example: amantadine, levodopa, etc.) and anti-dizziness agents (example: diphenidol, betahistine, etc.), can be used, and although it changes with combination objects, 0.1 - 10% of the weight of loadings are usually preferably used to drugs as an amount effective in a therapy. Moreover, when the inconvenience by the interaction does not arise, two or more kinds of concomitant use is also possible for these drugs if needed.

[0013] In the conventional acrylic independent basis, the bleedoff of the high drug which is not obtained of the combination of the styrene-isoprene-styrene block copolymer in the percutaneous absorption basis of this invention and/or a polyisobutylene, a softener, a tackifier, hexylene glycol, and l-menthol is attained, and, moreover, it can acquire high skin permeability. Moreover, since hexylene glycol does not dissolve substantially, or can use a basis component especially a styrene-isoprene-styrene block copolymer, and/or a polyisobutylene in the range in which the substantial dissolution is not obtained and can use them in the range which does not affect physical properties about l-menthol, either, good cohesive force and stability can be acquired.

[0014] The content to the pharmaceutical preparation whole quantity of these indispensable components is as follows. 10 - 40 % of the weight of styrene-isoprene-styrene block copolymers, Still more preferably 15 to 30% of the weight preferably 17 - 23 % of the weight, Still more preferably 2.5 to 7% of the weight preferably 2 - 10 % of the weight of polyisobutylenes 3 - 5 % of the weight, The combination of this range has [10 - 60 % of the weight of softeners] the effectiveness of this invention most at 25 - 50 % of the weight still more preferably 23 to 57% of the weight preferably 20 - 60 % of the weight of tackifiers 15 to 50% of the weight still more preferably 12 to 55% of the weight.

[0015] If there are few styrene-isoprene-styrene block copolymers and/or polyisobutylenes than the above-mentioned range, cohesive force will become inadequate, if [than the range] more, there will be little flexibility of pharmaceutical preparation and a problem will arise in adhesion. If there are few softeners than the range, there will be little flexibility of pharmaceutical preparation, a problem will arise in adhesion, and if [than the range] more, although flexibility becomes large, a problem will produce it in pharmaceutical preparation cohesive force. A tackifier has compatibility with hexylene glycol and l-menthol. If there are few tackifiers, sufficient combination of hexylene glycol and l-menthol cannot be performed, and sufficient absorption facilitatory effect by hexylene glycol and l-menthol will not be acquired.

[0016] Although it is known that the hexylene glycol which is the component of this

invention will be used as a moisturizer and an antimicrobial agent as a cosmetics raw material, it is necessary to blend amount sufficient as absorption enhancers of a drug effect component in this invention, and the loadings are 2 - 7 % of the weight more preferably 1.5 to 8% of the weight one to 10% of the weight. One or less % of the weight of loadings is [stabilization and the absorption facilitatory effect of basis physical properties] insufficient, and the bleeding by hexylene glycol arises at 10 % of the weight or more. Although the absorption facilitatory effect is checked conventionally, multiplication-effectiveness produces the l-menthol used as absorption enhancers with hexylene glycol with combination with hexylene glycol. The loadings are 1 - 5 % of the weight more preferably 0.5 to 6% of the weight 0.1 to 7% of the weight. 0.1 or less % of the weight of loadings is [an absorption facilitatory effect] insufficient, and lowering of the cohesive force of a basis component arises at 7 % of the weight or more.

[0017] If it considers as hexylene glycol and the rate of a compounding ratio of l-menthol, the absorption facilitatory effect of a drug has few rates of hexylene glycol:l-menthol 1:0.1 or less, and the bleeding of hexylene glycol and the cohesive force of a plaster body decline [the blending ratio of coal of hexylene glycol:l-menthol] or more by 1:7. this invention -- hexylene glycol: -- effectiveness is acquired for the rate of l-menthol by 1:0.1-1:7, the more desirable highest absorption facilitatory effect in 2:1-7:5 is acquired, and it becomes good also in respect of physical properties.

[0018] The anhydrous plaster of the pharmaceutical form of the percutaneous absorption patches of this invention in which plaster does not contain water substantially desirable especially is desirable. As a styrene-isoprene-styrene block copolymer, the styrene-isoprene-styrene block copolymer made from for example, shell chemistry (trade name: caliph REXX TR-1107, caliph REXX TR-1111), the styrene-isoprene-styrene block copolymer (trade name: JSR5000, JSR5100) by Japan Synthetic Rubber Co., Ltd., the styrene-isoprene-styrene block copolymer (trade name: Queen tuck 3421) by Nippon Zeon Co., Ltd., etc. are mentioned. As a polyisobutylene, the polyisobutylene made from for example, exon chemistry (trade name: Vistanex), the polyisobutylene made from BASUFU (trade name: Oppanol), etc. are mentioned.

[0019] As a softener, softeners, such as a liquid paraffin, polybutene, castor oil, cotton seed oil, palm oil, palm oil, and process oil, are illustrated. As a tackifier, alicycle group saturated hydrocarbon resin (for example, Al Cong P-100 (trade name)), Rosin ester (for example, KE-311, KE-100 (trade name), super ester S-100 (trade name)), A hydrogen alicycle group system hydrocarbon (for example, S KORETTSU 5300 (trade name)), Tackifiers, such as terpene system hydrogenation resin (for example, chestnut ARON P-105 (trade name)), hydrogenation rosin ester (for example, FORARU 105 (trade

name)), and dibasic-acid denaturation rosin ester (for example, pentalin 4741 (trade name)), are illustrated. These tackifiers can also mix and use two or more kinds if needed.

[0020] Next, the film used as the base material of this invention needs to have properties, such as excelling in the so-called barrier property for prevention of a break through, vaporization, and adsorption of drugs. Moreover, it is desirable that there is moderate flexibility at the time of sticking equipment on the skin. Although especially definition will not be carried out as a raw material of a base material if it has the above-mentioned conditions, aluminum, an ethylene vinyl acetate copolymer or its saponification object, cellulose acetate, a cellulose, nylon, polyester, polyethylene, a polyvinylidene chloride, a polycarbonate, polyvinyl alcohol, polypropylene, etc. are specifically raised as an example. These raw materials can carry out the laminating of what made the shape of a film or was made paper and blanket-like if needed to a film, can process it in the shape of a laminated film, or can process the vacuum plating of aluminium, ceramic vacuum evaporationo, etc., and can improve barrier property etc.

[0021] About the film used as a separator layer, it must be required during preservation of equipment to be able to prevent the break-through vaporization from a drugs layer etc., and exfoliation clearance must be possible for this separator layer in the case of the activity of equipment. The raw material of a separator film has aluminum, a cellulose, polyester, polyethylene, usable polypropylene, etc., and may specifically carry out the laminating of these films if needed. Moreover, the front face is processed by silicon or fluorocarbon, or a well-known additive is blended into a liner raw material, detachability may be adjusted or barrier property may be adjusted. The tongue section for exfoliation can be prepared in a separator so that the handling at the time of exfoliating may become easy.

[0022] Furthermore, a well-known additive can be blended if needed for preparation of an adhesive property, safety, and stability. Specifically SUMIKAGERU SP-520 (trade name), AKUA keeping 10SH (trade name), Water absorbing polymers, such as ARASOBU 800F (trade name) and SANWETTO 1M-1000MPS (trade name), Inorganic bulking agents, such as a zinc oxide, a calcium carbonate, a titanium dioxide, and silicas, Optimum dose content of citric-acid triethyl, a polyethylene glycol, the glycerol, etc. is suitably carried out as fatty alcohol, such as a cull call (trade name), and a moisturizer as a dissolution assistant as absorption enhancers of others, such as a glycerine fatty acid ester, crotamiton, etc., such as EKISERU (trade name).

[0023] Next, the manufacture approach of the percutaneous absorption pharmaceutical preparation of this invention is explained. or [it adding a drug-effect component,

hexylene glycol, and l-menthol, being mixed to homogeneity, cutting it if needed in the configuration of the bonnet request to the above-mentioned base material with an after / **** / liner, and making it with a product, after the percutaneous-absorption pharmaceutical preparation of this invention carries out the heating dissolution of all the basis components except for example, a drug-effect component, hexylene glycol, and l-menthol] -- or a sticking-by-pressure imprint can carry out after **** at a suitable base material at the film with which exfoliation processing was once performed, and it can also make with a product. Moreover, after dissolving all components in organic solvents, such as a hexane, toluene, and ethyl acetate, after **** and an organic solvent are removed to the above-mentioned base material, a liner cuts in a bonnet and a desired configuration, and it makes with a product, or an organic solvent can be removed after **** on the film with which exfoliation processing was once performed, a sticking-by-pressure imprint can be carried out at a suitable base material, and it can also make with a product.

[0024]

[Example] Although an example and the example of a trial are given and the percutaneous absorption patches of this invention are hereafter explained more to a detail, this invention is not limited to these examples. In addition, all the numeric values in an example, the example of a comparison, and the example of reference are weight %s.

[0025]

Example 1 Styrene-isoprene-styrene block copolymer 10 Liquid paraffin 60 Tackifier (alicycle group saturated-hydrocarbon resin 20 trade name: Al Cong P-100)

A polyisobutylene 7.3 Hexylene glycol 1 L-menthol 0.1 Dibutylhydroxytoluene 1 Estradiol 0.1 Norethisterone 0.5 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and norethisterone mixing pharmaceutical preparation.

[0026]

An example 2 A styrene-isoprene-styrene block copolymer 40 A liquid paraffin 10 Tackifier (rosin-ester trade name: KE-311) 15 A polyisobutylene 2 Hexylene glycol 10 L-menthol 7 Dibutylhydroxytoluene 1 Estradiol 5 Acetic-acid norethisterone 10 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0027]

Example 3 Styrene-isoprene-styrene block copolymer 19.5 Liquid paraffin 15 Tackifier

(hydrogenation rosin-ester 60 trade name: FORARU 105)
Hexylene glycol 1 L-menthol 0.5 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0028]

Example 4 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 35.4 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 8.6 Hexylene glycol 2 L-menthol 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0029]

Example 5 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 28 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 10 Hexylene glycol 7 L-menthol 1 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0030]

Example 6 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 31 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 5 Hexylene glycol 7 L-menthol 3 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0031]

Example 7 Styrene-isoprene-styrene block copolymer 23 Liquid paraffin 31 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 4 Hexylene glycol 1 L-menthol 7 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0032]

Example 8 Styrene-isoprene-styrene block copolymer 23 Liquid paraffin 19.9 Tackifier (hydrogenation rosin-ester 40 trade name: FORARU 105)

A polyisobutylene 3 Hexylene glycol 10 L-menthol 0.1 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0033]

Example 9 Styrene-isoprene-styrene block copolymer 17 Liquid paraffin 44 Tackifier (hydrogenation rosin-ester 25 trade name: FORARU 105)

A polyisobutylene 4 Hexylene glycol 3 L-menthol 3 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0034]

Example 10 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 35 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)

A polyisobutylene 5 Hexylene glycol 2 L-menthol 4 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0035]

Example 11 Styrene-isoprene-styrene block copolymer 18 Liquid paraffin 30 Tackifier (hydrogenation rosin-ester 34 trade name: FORARU 105)

A polyisobutylene 4 Hexylene glycol 6 L-menthol 4 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0036]

Example 12 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 26 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)

A polyisobutylene 10 Hexylene glycol 7 L-menthol 3 Dibutylhydroxytoluene 1 Ketoprofen 3 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as ketoprofen pharmaceutical preparation.

[0037]

Example 13 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 26 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)

A polyisobutylene 10 Hexylene glycol 7 L-menthol 3 Dibutylhydroxytoluene 1 Oxybutynin 3 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as oxybutynin pharmaceutical preparation.

[0038]

Example 14 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 26 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)

A polyisobutylene 10 Hexylene glycol 7 L-menthol 3 Dibutylhydroxytoluene 1 Fentanyl citrate 3 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as fentanyl citrate pharmaceutical preparation.

[0039]

The example 1 (hexylene glycol un-blending) of a comparison

Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 31 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)

A polyisobutylene 5 L-menthol 10 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0040]

The example 2 (l-menthol un-blending) of a comparison

Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 26 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)

A polyisobutylene 5 Hexylene glycol 15 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0041]

The example 3 (acrylic basis) of a comparison

TS-620 (product made from Japanese carbide) 94 L-menthol 3 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0042]

The example 4 (acrylic basis) of a comparison

TS-620 (product made from Japanese carbide) 90 Hexylene glycol 7 Estradiol 1

Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0043]

The example 5 (acrylic basis) of a comparison

TS-620 (product made from Japanese carbide) 87 Hexylene glycol 7 L-menthol 3 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0044] The actuation which presses a finger for about 1 second and pulls apart cohesive force, a finger tuck, and bleeding in a plaster body side per test piece of the test piece of the example of the example trial of trial 1. pharmaceutical preparation physical-properties examples 1, 2, 3, 6, 7, 12, 13, and 14 and the examples 1 and 2 of a comparison was repeated 5 times in the same location, and it evaluated from the condition of the plaster body side at that time. The result is shown in a table 1.

[0045]

[A table 1]

[0046] "O mark in a table 1 is very fitness" is shown, it is shown that O mark is "fitness",

"** mark is a defect a little" is shown, and it is shown that x mark is a "defect." an example -- cohesive force, a tuck, and bleeding -- although neither was problematic, in the example 1 of a comparison, the problem was accepted in cohesive force, in the example 2 of a comparison, bleeding was accepted and lowering of a finger tuck was accepted.

[0047] Skin irritation study was performed by the following technique per test piece of the test piece of the example of trial 2. skin-irritation-study examples 2, 6, 7, 12, 13, and 14, and the examples 1, 3, 4, and 5 of a comparison. Skin irritation was evaluated, after sticking the test piece on ten test subjects' (healthy people, male) overarm section and sticking on it for 24 hours. The result is shown in a table 2.

[0048]

[A table 2]

[0049] A high result of a skin stimulus was brought in the examples 1, 3, 4, and 5 of a comparison.

[0050] Hair loess mouse (6-weeks old, female) regions-of-back skin temperature (C) radiographic examination of 37 degrees was performed using the Franz mold diffusion cel per test piece of the example of trial 3. skin radiographic examination examples 2, 6, 7, and 11, and the examples 1, 2, and 5 of a comparison. Receptor liquid was extracted

for every after [test initiation] predetermined time, receptor liquid was filled up immediately after that, and the amount of transparency of the drug to extraction receptor liquid was measured by high-speed liquid chromatography. It made the measurement size of each test piece into three pieces at a time, respectively. The maximum transmission rate of estradiol (E2) and acetic-acid norethisterone (NETA) is shown in a table 3.

[0051]

[A table 3]

[0052] The thing of an example showed good drug permeability compared with the test piece of the example of a comparison.

[0053]

[Effect of the Invention] Thus, the percutaneous absorption pharmaceutical preparation of obtained this invention, and by blending hexylene glycol and l-menthol, percutaneous absorption patches raise the skin permeability of a drug effect component efficiently, and have the outstanding effectiveness of the stability of a basis, good cohesive force, low skin irritation, and high skin permeability preferably. After sticking the percutaneous absorption patches of this invention to the patient skin, the drugs of an amount effective in a therapy are absorbed from the skin correctly and certainly. Moreover, a merit since the degree of freedom of a drugs presentation is high, when the percutaneous absorption pharmaceutical preparation of this invention designs suitably skin permeability with a high drug effect component, the stability of a basis, and the effectiveness on a therapy is large.

[Translation done.]